Efficacy and safety of rupatadine in Japanese patients with seasonal allergic rhinitis: A double-blind, randomized, multicenter, placebo-controlled clinical trial

Kimihiro Okubo a,*, Takamasu Suzuki b, Ayaka Tanaka b, Hiroshi Aoki b

a Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan
b Teikoku Seiyaku Co., Ltd., Kagawa, Japan

ABSTRACT

Background: Rupatadine is a novel non-sedating second-generation H1-antihistamine with antiplatelet-activating factor activity, first marketed in Spain in 2003. It is used for treating allergic rhinitis in more than 80 countries. This study investigated its efficacy and safety in Japanese patients with seasonal allergic rhinitis (SAR).

Methods: This was a randomized, placebo-controlled, double-blind study conducted at 4 medical institutions in Japan (JapicCTI-152785). Adolescent and adult SAR outpatients aged 12–64 years entered a 1-week placebo run-in period. After eligibility was confirmed, patients orally received placebo, rupatadine 10 mg, or rupatadine 20 mg once daily for 2 weeks. The primary endpoint was a change from baseline to second week of treatment in total 4 nasal symptom score (T4NSS).

Results: Nine hundred patients were randomly assigned to placebo, rupatadine 10 mg, or rupatadine 20 mg (302, 298, and 300 patients, respectively). The least squares mean difference in the primary endpoint between rupatadine and placebo was 1.085 for 10 mg, and 1.415 for 20 mg (analysis of covariance, both *P* < 0.001). The rates of adverse events were 6.6%, 14.1%, and 15.0% for placebo, rupatadine 10 mg, and rupatadine 20 mg, respectively. Somnolence was most frequently reported: 7.0% for rupatadine 10 mg and 7.3% for rupatadine 20 mg. No serious adverse drug reactions were observed, and no adverse events resulted in premature discontinuation.

Conclusions: Rupatadine 10 and 20 mg were significantly superior to placebo in improving nasal and ocular symptoms of SAR, and were well tolerated.

Introduction

Allergic rhinitis is a very common chronic condition, affecting more than 500 million individuals worldwide. Although the etiology of allergic rhinitis is multifactorial, it can be classified as seasonal or perennial depending on the type of allergens and duration of symptoms. Seasonal allergic rhinitis (SAR) is an immunoglobulin E (IgE) antibody–mediated inflammatory
disorder. In Japan, cedar pollen grains (Cryptomeria japonica) are a major cause of SAR (pollinosis), with the prevalence of 26.5% of the Japanese population in 2008, characterized by sneezing, rhinorrhea, nasal congestion, and nasal itching. Such nasal conditions often compromise sleep quality, activities of daily living (ADLs), and quality of life (QoL).

In sensitized individuals, nasal mucosal exposure to allergens activates mast cells to release a variety of proinflammatory molecules, such as histamine, leukotriene, prostaglandin D2, thromboxane A2, and platelet-activating factor (PAF). These mediators recruit eosinophils, neutrophils, and other inflammatory cells that cause nasal symptoms. Treatment options for SAR include environmental control, pharmacotherapy, and allergen immunotherapy. Because it is practically impossible for patients with SAR to completely avoid allergen exposure, antihistamine therapy is a common option for symptom relief.

Of the four known histamine receptors, H1 receptors mediate the actions of histamine in allergic response, and H1 antagonists are widely used as treatment for allergic disorders. First-generation H1 antihistamines readily pass into the brain and interfere with histaminergic transmission to cause somnolence, sedation, fatigue, and cognitive impairment. Second-generation H1 antihistamines are minimally sedative and highly selective, and do not exhibit anticholinergic activity.

Rupatadine is a novel second-generation H1 antihistamine first discovered by J. Uriach y Cia S.A., Barcelona, Spain. Since its 2001 approval in Spain for the indication of allergic rhinitis, rupatadine has been marketed in more than 80 countries worldwide, and its indication was later expanded to include urticaria. This drug was also authorized for marketing in Japan in September 2017. The molecular structure of rupatadine is characterized by its piperidinyl and lutidinyl components. These components antagonize histamine H1 and PAF receptors, underlying rupatadine’s dual mechanism of action. PAF is a phospholipid mediator that induces increased vascular permeability, smooth muscle contraction, and neutrophil activation. Because PAF is involved in the occurrence of nasal congestion, rhinorrhea, and other allergic conditions, inhibition of the PAF signaling pathway can be a promising modality for treating allergic symptoms.

The pharmacokinetic and pharmacodynamic profile of rupatadine indicates that this drug is a fast-acting, once daily therapy. Following oral ingestion in humans, rupatadine is readily absorbed and reaches the peak plasma concentration with a median time to peak concentration (t\text{max}) of 0.67–1.00 h. Rupatadine exhibits high plasma protein binding property and extensive tissue distribution. Furthermore, desloratadine and its hydroxylated metabolites are some of the rupatadine metabolites that contribute to the drug’s overall efficacy. In fact, desloratadine is an antihistamine with a long half-life of 27 h. These facts suggest rapid onset and extended duration of efficacy.

The efficacy and safety of rupatadine have been established in overseas populations. We conducted a Phase 3 clinical trial to confirm its efficacy and safety in Japanese patients with SAR.

**Methods**

**Study design**

This was a multicenter, randomized, placebo-controlled, double-blind study in adolescent (12–17 years) and adult (18–64 years) outpatients with SAR. This study was conducted to evaluate the efficacy and safety of rupatadine at 4 medical institutions in Japan from February to May 2015.

The study procedures are schematically outlined in Figure 1. This study consisted of a 1-week single-blind run-in period and a 2-week double-blind treatment period. During the run-in period, all subjects were given placebo. Once eligibility was confirmed at the end of the run-in period, subjects were randomly assigned in a 1:1:1 ratio to receive placebo, rupatadine 10 mg, or rupatadine 20 mg once daily for 2 weeks. To ensure equal proportions of adolescents across the treatment arms, the permuted block method was used for randomization with age as a stratification factor. Randomization was performed using the EDC system: creation and management of key-coding was conducted by a third party, independent to the investigator or the sponsor. This clinical trial required subjects to make 5 study visits. At Visit 1, investigators screened patients for eligibility. At Visit 2, investigators registered eligible patients into the run-in period. At Visit 3 (Day 0), investigators enrolled patients and prescribed the first week’s study medication to start the treatment from the next day. At Visit 4, investigators dispensed study medication for the second week of treatment and monitored subjects’ drug adherence. At Visit 5, investigators made final safety and efficacy assessments.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice regulations and other regulatory requirements and was approved by the institutional review board (3 study sites: 394CLI, 1 study site: 566PIII) at each participating medical center. All adult patients gave written informed consent before initiation of any study-specific procedures. All minor patients gave written informed assent, and their legal representatives signed the written informed consent form. Patient anonymity was preserved using methods approved by the institutional review board. Prior to the time of first patient enrollment, this study was registered (Japan Pharmaceutical

![Fig. 1. Outline of study procedures.](image-url)
Participants

Outpatients satisfying the following requirements were included in the study: (i) age of 12–64 years at the time of signed informed consent, (ii) typical allergic rhinitis symptoms observed during the last 2 or more cedar pollen seasons, (iii) positive for cedar pollen–specific IgE antibodies (assessed as Classes 2 or greater using CAP-RAST [capsulated hydrophilic carrier polymer radioallergosorbent test], AlaSTAT® 3 g assay, or other methods), (iv) 4 nasal symptoms (sneezing, rhinorrhea, nasal congestion, and nasal itching) observed for 3 consecutive days before the start of study treatment, with a 3-day mean total 4 nasal symptom score (T4NSS, defined in the “Study endpoints and assessments” section below) of 6 or greater (i.e., a minimum 3-day sum of 18), (v) able to complete the patient diary appropriately and without errors, and (vi) informed consent signed by the patient (age ≥ 20 years) or legal representatives (age < 20 years; signed informed assent was also required for minor participants).

Patients meeting any of the following criteria were excluded from the study: (i) nasal diseases (e.g., nasal polyps, nasal septum deviation, or hypertrophic rhinitis); and infectious diseases (e.g., upper respiratory tract inflammation, sinusitis, infectious rhinitis, or infectious eye disease) that were likely to interfere with efficacy evaluation, (ii) current or history of nonallergic rhinitis (e.g., vasomotor, infectious, or drug-induced), (iii) history of intranasal laser coagulation or surgical treatment of nasal condition within 1 year before providing informed consent, (iv) severe or uncontrollable mild to moderate bronchial asthma requiring injectable, oral, or inhaled forms of steroids, (v) history of hypersensitivity to rupatadine, other antihistamines, or any of the components of the study tablets, (vi) current or previous use of desensitization therapy (within 3 years prior to screening), and (vii) severe hepatic or renal insufficiency. In addition, patients incapable of maintaining freedom from the following were excluded from the study:

- (a) psychotrophic drugs (tranquilizers, antipsychotics, antischizophrenia drugs, and antidepressants), nebulizers, eye drops, eye irrigation, nasal irrigation, cytochrome P450 (CYP) 3A4 inhibitors (e.g., ketoconazole and other synthetic antifungal azoles, erythromycin, and other macrolide antibiotics), CYP3A4 inducers (e.g., rifampicin and phenytoin), grape fruit juice, and products containing St. John’s Wort from the start of the run-in period to the end of study treatment

- (b) antihistamines (excluding antihistamine preparations for non-opthalmic and non-intranasal application and H2 blockers), leukotriene receptor antagonists, antithromboxane A2 agents, chemical mediator release inhibitors, TH2 cytokine inhibitors, external steroids (application of topical steroids to areas other than ocular and intranasal regions was permitted), vasoconstrictors (ocular or nasal), parasympatholytics (anticholinergics), and biologics (e.g., histamine-fixed human immunoglobulin preparation), immunosuppressants, and agents with pharmacological effect similar to any of the foregoing (e.g., herbal products believed to have antihistaminic or antiallergic properties) from 1 week before the start of the run-in period to the end of study treatment

- (c) steroid preparations (oral, injectable, or inhaled) from 3 weeks before the start of the run-in period to the end of study treatment

Study endpoints and assessments

In this clinical trial, the following efficacy variables were evaluated: T4NSS, total 2 ocular symptom score (T2OSS), total symptom score (TSS), symptom scores for sneezing, rhinorrhea, nasal congestion, nasal itching, eye itching, and tearing, ADL impairment score, rhinoscopy findings (swelling and color tone of the inferior turbinate mucosa, watery secretion volume, and type of nasal discharge), and patient and physician clinical overall impression scores. Each subject entered the severities of their sneezing, rhinorrhea, nasal congestion, nasal itching (4 nasal symptoms), eye itching and tearing (2 ocular symptoms), and ADL impairments, into his or her patient diary daily, using a 5-point grading scale ranging from 0 to 4 (Supplementary Table 1). The T4NSS and T2OSS scores were calculated daily by summing up the severity scores of the 4 nasal symptoms and 2 ocular symptoms, respectively. The TSS score was defined as the sum of the T4NSS and T2OSS scores. Subjects and investigators assessed the clinical overall impression of the effect of the study treatment at Visit 5 or earlier discontinuation using a 6-point scale: 1 = extremely improved, 2 = very improved, 3 = moderately improved, 4 = no change, 5 = worsened, and 6 = not evaluable.

The primary efficacy endpoint was the change from baseline in mean T4NSS score to the second week of treatment (6-day mean of Day 8 to Day 13 scores). The baseline T4NSS score was calculated as a mean of the last 3 days before the start of treatment (Day −3 to Day −1).

Secondary efficacy endpoints included: i) treatment-related changes from baseline in T4NSS, T2OSS, TSS, individual symptom scores, and ADL impairment scores evaluated for different time points and treatment durations (e.g., first 3 days, first week, and second week of treatment), ii) patient and physician clinical overall impression of change, and iii) change from baseline (Visit 3) in Japan Rhinoconjunctivitis Quality of Life Questionnaire (JrQoL) score at the end of study treatment (Visit 5) or earlier discontinuation.

Subject safety was assessed based on clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements (systolic and diastolic pressures and pulse rates), and adverse events that developed after the start of study treatment. Clinical laboratory tests were centrally analyzed (BML General Laboratory, Saitama, Japan). Measurement values outside the reference ranges of the contract testing laboratory were labeled as abnormal. Clinically significant abnormalities were reported as adverse events. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.16 Grades were determined using the Common Terminology Criteria for Adverse Events, Version 4.0.17 Adverse events having at least a reasonable possibility of causal association with the study were classified as adverse drug reactions.

Statistical methods and analysis sets

The sample size of approximately 900 subjects (300 patients/arm) was determined based on the results of a prior overseas Phase 3 clinical trial of rupatadine in SAR patients. In the overseas Phase 3 clinical trial, the change from baseline in T4NSS score to the second week of treatment was −3.9 for placebo and −4.5 for rupatadine 10 mg. Simulations showed that 295 subjects per arm should be included to detect the between-arm difference at a statistical power of 0.8, assuming a common standard deviation of 2.6 and a one-sided significance of 0.025.

Subject safety was assessed in the safety analysis set (SAS), which included all subjects who took at least 1 dose of the study medication. Efficacy analyses were based on the full analysis set.
The primary efficacy endpoint was analyzed by employing the analysis of covariance (ANOVA) model, with the baseline score as the covariate and the treatment arm and age group as the factors. In addition, the least squares mean changes from baseline to the second week of treatment were computed for individual arms. The superiority of rupatadine 10 mg and 20 mg to placebo was tested at a one-sided 0.025 significance. The closed testing approach was adopted for multiplicity adjustment in which rupatadine 10 mg was compared with placebo first. The comparison between rupatadine 20 mg and placebo was to be implemented if rupatadine 10 mg was shown to be superior to placebo.

Changes from baseline in T2OSS, TSS, and individual symptom scores were analyzed using the ANCOVA model, in a manner similar to the primary efficacy analysis. Clinical overall impression scores were compared between rupatadine and placebo using the Wilcoxon two-sample test. Changes in the JRQLQ total and subscale scores between rupatadine versus placebo were analyzed using the ANCOVA model. In addition, posthoc analyses were conducted to evaluate (i) between-arm differences in the primary endpoint by baseline subgroups, (ii) changes from baseline in T4NSS by the treatment arm, and (iii) differences in the JRQLQ subscale and domain scores by the treatment arm. Multiplicity adjustment was not performed in secondary efficacy analyses.

Results

Participants

A total of 1266 patients underwent screening for study eligibility, and 1176 patients completed the preliminary registration and entered into the run-in period. Nine hundred patients were randomized to start the study medication, with 302, 298, and 300 subjects assigned to receive placebo, rupatadine 10 mg, and rupatadine 20 mg, respectively. Seven subjects prematurely discontinued the study. The reasons for discontinuation were: consent withdrawal, nonmedical cause, and other. The disposition of study subjects is schematically illustrated in Figure 2.

The FAS and SAS populations of this clinical trial were identical (hereinafter referred to as the “study population”). In the study population, 37 (12.3%), 35 (11.7%), and 36 (12.0%) adolescent subjects were treated with placebo, rupatadine 10 mg, and rupatadine 20 mg, respectively. The mean age was 36.7 years, and 457 males (50.8%) were included in this study. Subjects were well balanced across the treatment arms with respect to the demographic and baseline characteristics examined (Supplementary Table 2). The mean exposure duration in patients treated with placebo, rupatadine 10 mg, and rupatadine 20 mg was 12.9, 12.9, and 13.0 days, respectively.

Primary endpoint

Rupatadine 10 mg and 20 mg significantly improved the primary endpoint compared with placebo (Table 1). The ANCOVA analyses showed that the least squares mean change from baseline in T4NSS score to the second week of treatment was $-0.604$ [95% CI: $-0.927$, $-0.281$] for placebo, $-1.689$ [95% CI: $-2.016$, $-1.362$] for rupatadine 10 mg, and $-2.019$ [95% CI: $-2.344$, $-1.693$] for rupatadine 20 mg (percent reduction from baseline: placebo, 6%; rupatadine 10 mg, 18%; and rupatadine 20 mg, 21%). The estimated difference between rupatadine and placebo was $-1.085$ [95% CI: $-1.465$, $-0.705$] for rupatadine 10 mg and $-1.415$ [95% CI: $-1.794$, $-1.035$] for rupatadine 20 mg. Rupatadine 10 mg and 20 mg doses were statistically superior to placebo (both $P < 0.001$). The results supported the hypothesis that rupatadine is superior to placebo in reducing nasal symptoms of SAR.

![Fig. 2. Disposition of study subjects. SAS indicates safety analysis set; and FAS, full analysis set.](image-url)
Table 1
Change from baseline in mean T4NSS score after 2 weeks of rupatadine and placebo treatment.

<table>
<thead>
<tr>
<th>Mean T4NSS Statistics</th>
<th>Placebo</th>
<th>Rupatadine, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>302</td>
<td>298</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.555 (2.454)</td>
<td>9.566 (2.367)</td>
</tr>
<tr>
<td>Minimum–Maximum</td>
<td>6.00–16.00</td>
<td>6.00–16.00</td>
</tr>
<tr>
<td>Second week of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>301</td>
<td>296</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.785 (2.657)</td>
<td>7.690 (2.712)</td>
</tr>
<tr>
<td>Median</td>
<td>8.667</td>
<td>7.500</td>
</tr>
<tr>
<td>Minimum–Maximum</td>
<td>1.83–15.25</td>
<td>1.17–16.00</td>
</tr>
<tr>
<td>Treatment-related change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>301</td>
<td>296</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-0.779 (2.460)</td>
<td>-1.863 (2.621)</td>
</tr>
<tr>
<td>Median</td>
<td>-0.667</td>
<td>-2.000</td>
</tr>
<tr>
<td>Least squares mean [95% CI]</td>
<td>-0.604 [-0.927, -0.281]</td>
<td>-1.689 [-2.016, -1.362]</td>
</tr>
<tr>
<td>Difference in least squares means [95% CI]</td>
<td>-0.105 [-1.465, -0.705]</td>
<td>-1.415 [-1.794, -1.035]</td>
</tr>
</tbody>
</table>

1. Difference between rupatadine 10 mg or 20 mg versus placebo.
2. The closed testing procedure was applied to test the differences between rupatadine 10 mg versus placebo and rupatadine 20 mg versus placebo in a step-wise manner at a one-tailed $P < 0.001$ or $P < 0.007$.

Posthoc subgroup analyses of the primary endpoint

Posthoc subgroup analyses by sex, cedar pollen–specific IgE class, geographical location (east and west Japan), and baseline T4NSS score showed that rupatadine 10 mg and 20 mg doses are superior to placebo in all subgroups investigated. Moreover, the results of the posthoc analyses of the primary endpoint by age (adult and adolescents) and baseline T4NSS score showed that rupatadine 20 mg was associated with greater least squares mean changes from baseline in T4NSS than rupatadine 10 mg in all subgroups investigated (Supplementary Table 3). However, no statistically significant difference was noted in the primary endpoint between 10 mg and 20 mg, except in the subgroup with a baseline T4NSS score of ≥14. In this subgroup, the least squares mean difference [95% CI] between 10 mg and 20 mg was −2.184 [-3.909, −0.459], which was of statistical significance ($P = 0.007$).

In adolescents, rupatadine 10 mg and 20 mg achieved a numerically greater T4NSS improvement than placebo, albeit not statistically significant ($P = 0.344$ and $P = 0.186$, respectively).

Secondary endpoints

Changes from baseline in T4NSS, T2OSS, TSS, and individual symptom scores in the first 3 days, first week, and second week of treatment are summarized in Table 2. Rupatadine 10 mg and 20 mg consistently yielded better results than placebo throughout the study. Comparison after 3 days of treatment showed notable differences in treatment response between rupatadine and placebo, and the superiority of rupatadine to placebo continued till the end of the clinical trial. ANOVA analyses of the changes from baseline at the second week of treatment showed that rupatadine 10 mg and 20 mg were statistically better than placebo for all endpoints tested ($P < 0.001$ or $P < 0.004$, Table 2).

Changes over time in T4NSS score are graphically illustrated in Figure 3 for placebo, rupatadine 10 mg and 20 mg. The clinical benefit of rupatadine was immediate, and rupatadine doses significantly improved the nasal symptoms, starting on Day 1. This means that the onset of action was observed 24 h after the first dose intake. The mean T4NSS score in subjects treated with rupatadine 10 mg and 20 mg showed a much greater decrease than that in those treated with placebo throughout the study. Changes from the baseline are graphically illustrated in Supplementary Figure 1.

Furthermore, the results of the patient and physician clinical overall impression (Supplementary Fig. 2) and QoL score (JRQLQ questionnaire, Supplementary Fig. 3) provide additional evidence of the superiority of rupatadine 10 mg and 20 mg doses over placebo. In the patient clinical overall impression, 129 (43.3%) and 147 (49.0%) subjects treated with rupatadine 10 mg and 20 mg, respectively, reported “extremely improved” or “very improved,” whereas only 83 (27.5%) of the subjects treated with placebo reported such results. The results showed a statistically significant difference between placebo versus rupatadine 10 mg and 20 mg groups (both $P < 0.001$). Changes from baseline to the second week of treatment in JRQLQ total score were significantly greater for rupatadine 10 mg and 20 mg than placebo (both $P < 0.001$). In addition, the results on the subscales I, II, and III (nasal and eye symptoms, QoL, and overall) and 6 domains (daily activities, outdoor activities, social functioning, sleep problems, general physical problems, and emotional function) of JRQLQ consistently showed that rupatadine 10 mg and 20 mg were superior to placebo, with the exception that no statistical significance was observed between rupatadine 10 mg versus placebo for sleep problems ($P = 0.271$) and general physical problems ($P = 0.414$).

Safety

Table 3 summarizes the reported adverse events and adverse drug reactions. There were no cases of death, serious adverse events, Grade 3 or higher adverse events, serious adverse drug reactions, or adverse events resulting in premature study discontinuation.

During the treatment period, adverse events were reported at a rate of 6.6% (20/302) with placebo, 14.1% (42/298) with rupatadine 10 mg, and 15.0% (45/300) with rupatadine 20 mg. These included adverse drug reactions reported at 4.3% with placebo, 11.1% with rupatadine 10 mg, and 11.7% with rupatadine 20 mg. Adverse events of malaise, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatinine phosphokinase, protein urine, and somnolence were noted at an incidence ≥1% in at least 1 of the treatment groups. Among these adverse events, 1 case of increased aspartate aminotransferase (rupatadine
Table 2
Change from baseline in efficacy variables by treatment: placebo, rupatadine 10 mg, and rupatadine 20 mg.

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Dose, mg</th>
<th>Baseline, mean [SD]</th>
<th>Change from baseline</th>
<th>Least squares mean [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean [SD]</td>
<td>First 3 days</td>
<td>First week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4NSS</td>
<td>0</td>
<td>9.555 [2.454]</td>
<td>-0.276 [2.367]</td>
<td>-0.274 [2.122]</td>
</tr>
<tr>
<td>T2OSS</td>
<td>0</td>
<td>4.301 [1.376]</td>
<td>-0.158 [1.274]</td>
<td>-0.180 [1.162]</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0</td>
<td>2.283 [0.793]</td>
<td>-0.076 [0.698]</td>
<td>-0.104 [0.626]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.292 [0.766]</td>
<td>-0.516 [0.777]</td>
<td>-0.497 [0.706]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.304 [0.809]</td>
<td>-0.604 [0.765]</td>
<td>-0.600 [0.724]</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0</td>
<td>2.096 [0.749]</td>
<td>0.007 [0.662]</td>
<td>0.026 [0.591]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.116 [0.723]</td>
<td>-0.275 [0.669]</td>
<td>-0.210 [0.614]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.190 [0.699]</td>
<td>-0.330 [0.660]</td>
<td>-0.301 [0.597]</td>
</tr>
<tr>
<td>Nasal itching</td>
<td>0</td>
<td>2.604 [0.727]</td>
<td>-0.148 [0.718]</td>
<td>-0.151 [0.655]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.548 [0.712]</td>
<td>-0.536 [0.778]</td>
<td>-0.496 [0.714]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.613 [0.725]</td>
<td>-0.640 [0.849]</td>
<td>-0.601 [0.777]</td>
</tr>
<tr>
<td>Eye itching</td>
<td>0</td>
<td>2.549 [0.743]</td>
<td>-0.149 [0.731]</td>
<td>-0.159 [0.650]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.594 [0.838]</td>
<td>-0.518 [0.796]</td>
<td>-0.495 [0.736]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.614 [0.807]</td>
<td>-0.529 [0.824]</td>
<td>-0.509 [0.766]</td>
</tr>
<tr>
<td>Tearing</td>
<td>0</td>
<td>1.753 [0.842]</td>
<td>-0.009 [0.669]</td>
<td>-0.020 [0.630]</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.841 [0.841]</td>
<td>-0.137 [0.681]</td>
<td>-0.309 [0.623]</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1.802 [0.853]</td>
<td>-0.386 [0.732]</td>
<td>-0.353 [0.682]</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the numbers of subjects evaluated. Rupatadine 0 mg dose = placebo. *P < 0.001 (ANCOVA, versus placebo). P = 0.004 (ANCOVA, versus placebo). T4NSS indicates total 4 nasal symptom score; T2OSS, total 2 ocular symptom score; TSS, total symptom score; and ANCOVA, analysis of covariance.

20 mg), 8 cases of increased blood creatinine phosphokinase (2 with placebo, 3 with rupatadine 10 mg, and 3 with rupatadine 20 mg), and 3 cases of protein urine (1 with rupatadine 10 mg and 2 with rupatadine 20 mg) were considered to be unrelated with the study drug. Somnolence was the most frequently reported adverse drug reaction to rupatadine, with an incidence rate of 7.0% (21/298) for rupatadine 10 mg and 7.3% (22/300) for rupatadine 20 mg. The incidences of somnolence were similar for rupatadine 10 mg and 20 mg, whereas somnolence was observed at a much lower rate in placebo-treated patients (0.7%, 2/302). Recovery was reported for all episodes of somnolence.

In subjects treated with rupatadine 20 mg, increased levels of alanine aminotransferase and aspartate aminotransferase were reported at a slightly higher rate than the incidence reported in
placebo-treated subjects. One case of increased aspartate aminotransferase in the 20 mg group was judged to be unrelated to the study drug because it was considered to be caused by excessive physical activity. Four subjects of the rupatadine 20 mg group who reported increased alanine aminotransferase also reported increased aspartate aminotransferase.

Grade 2 adverse drug reactions occurred at a rate of 0.7% in the rupatadine 10 mg group (2/298, somnolence and rash) and 0.3% in the rupatadine 20 mg group (1/300, headaches). Other adverse drug reactions were classified as Grade 1.

The incidences of adverse drug reactions were compared by age. Discrepancies in incidence between adolescent and adult subjects were noted for the following: malaise (0/108 versus 5/792), increased alanine aminotransferase (0/108 versus 5/792), increased aspartate aminotransferase (0/108 versus 4/792), and urine protein (3/108 versus 5/792). However, the low frequencies of these adverse drug reactions did not allow for description of a definite pattern (Supplementary Table 4).

**Discussion**

This is the first placebo-controlled clinical trial to demonstrate that rupatadine is efficacious and safe for treating Japanese patients with SAR. The primary and secondary efficacy outcome showed that both rupatadine 10 mg and 20 mg are superior to placebo in alleviating nasal and ocular symptoms in patients with SAR.

Safety outcomes suggesting that rupatadine 10 mg and 20 mg doses were well tolerated. This clinical trial provided robust evidence for the clinical benefits of rupatadine therapy in treating the Japanese patients with SAR.

The primary efficacy endpoint T4NSS evaluated the major 4 nasal symptoms of SAR: sneezing, rhinorrhea, nasal congestion,
and nasal itching. These symptoms were selected based on national and international guidelines for allergic rhinitis management.\textsuperscript{18,3,4,6,19–22}

The results of subgroup analyses of the primary efficacy outcomes indicated that rupatadine is effective in treating SAR regardless of the patients’ age, geographical location, sex, and baseline disease severity. The absence of statistical significance in the adolescent subgroup was most likely due to the fact that sample size required for the intergroup comparison of efficacy in adolescents was not considered in our study; our study considered the sample size required for evaluating the efficacy of study drug groups to placebo (300 subjects, each). In addition to the above, the higher severity of the baseline T4NSS in adolescents (baseline T4NSS ≥ 12: adults, 145/792 [18.3%]; adolescents, 30/108 [27.8%]) may have interfered with the results. The findings in the study population are generally applicable to the adolescent population.

Fast onset of action is highly desirable for antihistamines.\textsuperscript{23} Onset of action of an allergic rhinitis drug may be defined as the point at which patients might reasonably expect to see a meaningful decrease in their symptoms.\textsuperscript{22} Rupatadine significantly reduced the T4NSS score as early as Day 1 of treatment in this clinical trial (Fig. 3). In a study by Muñoz-Cano \textit{et al.}, rupatadine showed a trend to decrease PAF-induced T4NSS from 60 to 120 min in SAR patients.\textsuperscript{10} Rupatadine’s fast onset of action is consistent with its short t\textsubscript{max} of 0.67 and 1.00 h following repeated doses at 10 mg and 20 mg, respectively.\textsuperscript{11}

The performance of rupatadine 20 mg was generally better than that of rupatadine 10 mg, although their differences were not statistically significant for most of the efficacy variables investigated. Changes from baseline to the second week of treatment were numerically greater for rupatadine 20 mg than for rupatadine 10 mg in T4NSS, T2OSS, TSS, and individual symptom scores, except for eye itching (Table 2). In addition, changes from baseline to the second week of treatment in the JRQLQ total score (Fig. 4), subscales I, II, III, and 6 domain scores (Supplementary Fig. 3) were comparatively greater for rupatadine 20 mg. Moreover, the proportions of subjects and investigators reporting “extremely improved” or “very improved” were moderately larger for rupatadine 20 mg (Supplementary Fig. 2). However, considering the general absence of marked efficacy differences, the starting rupatadine dose should be 10 mg for most patients from a safety perspective. Rupatadine 20 mg can be a viable therapy for patients with severe SAR symptoms. This option is supported by the finding that rupatadine 20 mg yielded a statistically better performance in alleviating nasal symptoms than rupatadine 10 mg in the subgroup of patients in the highest baseline disease severity category (T4NSS ≥ 14).

Improvements in nasal and ocular symptoms can help increase the QoL of patients with SAR.\textsuperscript{24} In this clinical trial, rupatadine significantly improved the JRQLQ total score. In domestic clinical studies in patients with allergic rhinitis, this questionnaire is often used because it has been tailored to suit the situations of Japanese patients.\textsuperscript{25} Internationally, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a commonly administered disease-specific assessment tool.\textsuperscript{26} The JRQLQ and the Japanese version of the RQLQ correlate well with each other with respect to the measurement of QoL of patients with cedar pollinosis.\textsuperscript{27} The favorable QoL results reported in patients treated with rupatadine in this clinical trial indicate that this agent is a favorable pharmacological management option for SAR.

In case of severe nasal symptoms, antihistamines are not selected as first-line agents for the treatment of allergic rhinitis.\textsuperscript{5} Rupatadine is a dual antagonist; although the current study was not designed for the evaluation on the anti PAF effect of the drug, recent studies have demonstrated the role of PAF inhibitor on nasal airways.\textsuperscript{8} We investigated the potential effect of rupatadine on nasal airways compared to other second-generation antihistamines. In the study with similar design evaluating the efficacy of bilastine, a second-generation anti histamine, evaluating nasal congestion in Japanese patients by Okubo \textit{et al.}, the reduction in the mean score for nasal congestion compared with placebo at Week 2 was −0.07.\textsuperscript{28} In a placebo controlled study evaluating nasal congestion in Japanese patients, desloratadine targeting patients with lower severity of nasal congestion, improvement in the score for the study drug group was less than 0.05 at Week 2.\textsuperscript{29} As in the premise, rupatadine performed better than the results mentioned above, scoring approximately −0.15 and −0.26 mean score reduction compared with placebo in the 10 mg and 20 mg groups, respectively. Although the comparison cannot be conclusive due to the fact that the results were derived from different studies, higher efficacy in improving nasal congestion is implicated for rupatadine than in non-PAF inhibiting agents. Findings above suggest the contribution of PAF inhibitory effect of rupatadine on the improvement nasal congestion.

Somnolence was the only nervous system adverse drug reaction to rupatadine with an incidence of 1.0% or greater. The results on the incidence of somnolence are consistent with the literature. In a review of patients treated with rupatadine 10 mg once daily (n = 2025) during clinical trials, Pico\textsuperscript{d} reported a frequency of 9.5% for somnolence.\textsuperscript{30} Headache (6.8%) and fatigue (3.2%) were also common adverse effects of rupatadine in the review. In this clinical trial, however, headache was documented only in 1 subject treated with rupatadine 20 mg, and no episodes of fatigue were reported.

A major limitation of this clinical trial was that the maximum duration of the study treatment was 2 weeks. The long-term risk–benefit profile of rupatadine in Japanese patients remains unknown. The fact that patients with SAR take medications for several months underscores the need for a longer clinical trial.\textsuperscript{11} Long-term rupatadine treatment options for allergic rhinitis will be informed by clinical investigation in patients with perennial allergic rhinitis.

In conclusion, we demonstrated that rupatadine 10 mg and 20 mg once daily for 2 weeks provided superior efficacy over placebo in Japanese adult and adolescent patients with SAR. Rupatadine doses were well tolerated. Given the absence of marked efficacy differences, the starting dosage for most patients should be 10 mg once daily. Rupatadine 20 mg can be a viable option for patients with severe symptoms.

\textbf{Fig. 4}. Changes from baseline in least mean square JRQLQ total score (95% CI) after 2 weeks of placebo, rupatadine 10 mg, and rupatadine 20 mg treatment. JRQLQ total scores are shown as the least mean square. $^*$P < 0.001 versus placebo.
Acknowledgements

This clinical trial was sponsored by Teikoku Seiyaku Co., Ltd., Kagawa, Japan. The sponsor has borne the costs for third-party writing assistance.

The authors appreciate the contribution of the following study investigators: Yoshihiro Ohashi (OPHAC Hospital, Osaka), Minoru Gotoh (ToCRoM Clinic, Tokyo), Yasuyuki Nomura (Koganeibashi Sakura Clinic, Tokyo), and Kazuhiro Hashiguchi (Shinanozaka Clinic, Tokyo). The authors thank Dr. Toshimitsu Hamasaki of the Sakura Clinic, Tokyo, and Kazuhiro Hashiguchi (Shinanozaka Clinic, Tokyo). The authors thank Dr. Toshimitsu Hamasaki of the National Cerebral and Cardiovascular Center, Osaka, Japan, for his statistical advice and Dr. Inaki Izquierdo Pulido of J. Uriach y CIA S.A. for scientific review of the manuscript. The authors acknowledge the technical assistance with monitoring of this clinical trial, data collection and management, and statistical analysis provided by Intellim Corp., Tokyo, Japan. Editorial assistance by Mr. Yusashi Sasaoka and staff members at SunFlare Co., Ltd., Tokyo, Japan, is also acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2018.08.011.

Conflict of interest
KO has received consultant fee from Teikoku Seiyaku, the sponsor of this study, Taiho Pharma, Mitsubishi Tanabe Pharma, Torii Pharmaceutical, Meiji Seika Pharma, and Kyorin Pharmaceutical. TS, AT, and HA are employees of Teikoku Seiyaku.

Authors’ contributions
KO contributed to literature search, study design, data analysis, and manuscript preparation. TS, AT, and HA contributed to the study design, data collection and interpretation, and manuscript review.

References
17. [Accessed 18 October 2018].